VII. Clinical Investigation

A. General

The requirements described in 21 CFR Part 812 apply to the clinical investigations of refractive implants.

B. Elements of the Clinical Protocol

The following are elements of a clinical protocol that may be used to collect sufficient, relevant and appropriate data to determine the safety and effectiveness of refractive implants.

1. Study Objectives

   The sponsor should outline the objectives of the clinical investigation. These objectives should include the collection of safety and effectiveness data to support a premarket approval application (PMA). The proposed indications for use of the RI should be stated.

   Note: Sponsors that intend to include mixed astigmatism as an indication should be aware that additional safety and/or efficacy endpoints and analyses may be required.

2. Risk/Benefit Analysis

   The risk/benefit analysis should provide a description and analysis of all risks to which the subjects will be exposed, how those risks will be minimized and a justification for the investigation. Additionally, the expected risks and benefits of the new device should be compared to other available options for refractive correction (such as RK, PRK, LASIK, spectacles, contact lenses).

3. Study Endpoints

   a. Safety Endpoints and Target Values

      The following safety endpoints and target values are only recommendations; certain refractive devices may pose different safety concerns and therefore, additional or fewer safety endpoints may be appropriate.

      <u>Maintenance of Endothelial Cell Counts</u>

      - Endothelial cell loss as measured between the preoperative and the Month 3 postoperative visit should not exceed 10%.

      - Endothelial cell loss between the Month 3 and Month 36 exam should be reported and should not exceed 4.125% (equivalent to 1.5% per year).

      <u>Maintenance of Best Spectacle-Corrected Visual Acuity (BSCVA)</u>

      - <5% of eyes should lose 2 lines or more BSCVA (or BCLVA, where appropriate - see Section 7 below)

- <1% of eyes should have BSCVA (or BCLVA, where appropriate - see Section 7 below) worse than 20/40 (if 20/20 or better BSCVA preoperatively)

Induced Manifest Refraction Cylinder

- For those RIs that are not intended to correct pre-existing cylinder, <1% of eyes should have an induced manifest refractive astigmatism of greater than 2 D of absolute cylinder.

Adverse events

- The rates of adverse events associated with refractive implants, including cataract formation, should be reported.

b. Effectiveness Endpoints and Target Values

The following effectiveness endpoints are only recommendations. Sponsors wishing to make an additional marketing claim (beyond the indication(s) supported by the following endpoints) should include additional effectiveness endpoint(s) to substantiate the claim.

Predictability of Refraction

- 75% of eyes should achieve predictability (attempted versus achieved) of the MRSE of ± 1.00 D

- 50% of eyes should achieve predictability (attempted versus achieved) of the MRSE of ±0.50 D.

Uncorrected Visual Acuity (UCVA)

- 85% of eyes should achieve an UCVA of 20/40 or better (for those eyes with BSCVA of 20/20 or better preoperatively).

4. Study Design

The study design, including the sample size, duration of the study, proposed phased enrollment, and any plans for fellow eye implantation should be described. FDA recommends that separate protocols be submitted for each indication to be studied (e.g., myopia, hyperopia, presbyopia, myopia with myopic astigmatism, mixed astigmatism, etc.).

a. Sample Size

i. Safety and Effectiveness Study

The sample size for this study should be adequate to evaluate the rates of adverse events associated with refractive implants. Experience with aphakic IOLs and their associated adverse event rates demonstrates that a sample size of 300 subjects provides adequate precision for adverse events occurring at rates of 0.1% or greater (see FDA Draft IOL Guidance, October 14, 1999 and ISO/DIS 11979-7, Annex B). The maximum number of subjects enrolled in any study should be limited to

no more than 143% of the sample size that the sponsor intends for the study.

After all of the subjects needed for a study have been enrolled, the sponsor may request approval to enroll additional subjects into a modified core study of the device so that investigators may continue their experience with the device until any premarket approval is obtained.

ii. Endothelial cell counts substudy

The loss of endothelial cells over time should be determined by evaluating measurements taken at the Month 3 (or Month 6) through Month 36 exams. The number of subjects should be sufficient to detect a yearly endothelial cell loss of 1.5% and to demonstrate linearity of the cell loss over time (see Section 9 below).

iii. Contrast sensitivity/low contrast acuity substudy

For the analysis of contrast sensitivity loss, a sample size of approximately 125 subjects is recommended (see Section 9 below).

b. Number of investigators

Each investigator should contribute a minimum of 20 subjects to the study population, but not more than 25% of the subjects in the study.

c. Study Duration

A study duration of three years is recommended to adequately evaluate the maintenance of endothelial cell counts and the rate of cataractogenesis.

d. Lost to follow-up

The lost to follow-up patients should comprise less than 10% of the study population after one year, and less than 30% of the study population after three years.

e. Enrollment

The following phased enrollment plans are recommendations only. Depending on the design of the refractive implant, a different phase-in may be recommended. For example, if a significant design change is required for an additional indication, a slower phase-in may be necessary.

Note: Sponsors may wish to provide a scientific rationale to begin enrollment with Phase II. This rationale may consist of results from well-documented clinical trials conducted outside of the U.S.

For clinical studies for a single refractive indication:

- Phase I - 10 subjects, followed for 6 months

- Phase II - 100 additional subjects, with a report to FDA when 50 subjects have been followed for 6 months and all 110 subjects have been enrolled
- Phase III - remainder of study population

For clinical studies of more than one refractive indication (e.g., myopia and hyperopia or myopia and myopia with myopic astigmatism) ongoing simultaneously:

- Phase I - 20 subjects (no more than 10 of each indication), followed for 6 months
- Phase II - 150 additional subjects (no more than 100 per indication). A request to expand the enrollment for one indication may be submitted when 50 subjects with that indication have been followed for 6 months. The report should include data for all subjects enrolled for the particular indication.
- Phase III - The remainder of the study population for an individual indication.

For clinical studies of RIs that provide astigmatic correction (in addition to a spherical correction), where substantial clinical data has been collected for the spherical correction:

- Phase II – 100 subjects, with a report to FDA when 50 subjects have been followed for 6 months and all 100 subjects have been enrolled.
- Phase III – remainder of the study population needed to demonstrate effectiveness of the cylindrical correction

f. Bilateral Implantation

FDA has concerns about exposing both eyes to a new device without some prior clinical safety information. Therefore, bilateral implantation should not be performed during Phase I. Sponsors should attempt to enroll contact lens tolerant subjects in the Phase I to avoid difficulties with anisometropia. The informed consent document should state clearly that bilateral implantation will not be available early in the investigation. A prospective protocol waiver may be submitted for bilateral implantation of a Phase I subject, but must contain a strong clinical rationale.

At the time that expansion to Phase III is approved, sponsors may wish to allow implantation of the fellow eye, under the following conditions:

- no adverse events in the initially implanted eye
- with a waiting period of 90 days between eyes
- with signed informed consent document specifically for fellow eye implantation

Sponsors may wish to provide additional information as a rationale for a shorter waiting period between eyes. Additionally, prospective protocol waivers may be submitted for those subjects for whom the investigator believes fellow eye implantation with less than 90 days between eyes is necessary.

g. Implant Exchanges

During the investigation, the implant may be removed (without replacement) at any time at the request of the subject or if the investigator believes it appropriate. However, FDA believes that implant exchanges should be limited in number so as to preserve the integrity of the clinical data and to prevent an undue lengthening of the study.

At the time that expansion to Phase III is approved, sponsors may wish to allow exchanges when certain criteria have been met. The criteria for exchanges should include a waiting period based on the point of refractive stability and any other longer-term safety concerns. Prior to Phase III, prospective protocol waivers may be submitted for those subjects for whom the investigator believes an implant exchange is necessary.

5. Study Population

The following are recommended inclusion criteria for studies of refractive implants:

- myopic subject is >18 years of age, < 45 (ideally) or 50 years of age (to avoid age-related cataract formation as a confounding variable)
- hyperopic subject is >18 years of age, <60 years of age (given the older average age of hyperopes and difficulties in enrollment)

  Note: Sponsors wishing to enroll hyperopic patients older than 50 should modify the informed consent document to note the increased likelihood of cataract formation with advancing age.

- subject meets specified refractive criteria (spherical and cylindrical components)
- subject has specified minimum BSCVA in each eye and UCVA 20/40 or worse
- hyperopic subject has less than 0.75 D difference between cycloplegic and manifest refraction
- subject has had a stable correction (± 0.5 D), as determined by MRSE for a minimum of 12 months prior to surgery, verified by consecutive refractions and/or medical records or prescription history.
- subject, whose current method of correction is contact lenses, has demonstrated a stable refraction (±0.5 D), as determined by MRSE, on two consecutive exam dates. Stability of the refraction is determined by the following criteria: a) lenses were not worn for at least 2 weeks (rigid and toric contact lenses) or 3 days (soft contact lenses) prior to the first refraction; b) the two refractions were performed at least 7 days apart. (Contact lens wearers must also have demonstrated preoperative stability as defined above.)
- subject, age 21-45, has at least 2500 endothelial cells as determined by specular microscopy; subject, age 46 or older, has at least 2000 endothelial cells as determined by specular microscopy
- subject, with a significant cylindrical refractive error, who would receive an RI providing spherical correction only, has been given the opportunity to experience his/her best spectacle vision with spherical correction only and is willing to proceed with the surgery
- subject has given written informed consent

- subject is willing and able to comply with schedule for follow-up visits

The following are recommended exclusion criteria for studies of refractive implants:

- subject has an acute or chronic disease or illness that would increase the operative risk or confound the outcome(s) of the study (e.g., immunocompromised, connective tissue disease, clinically significant atopic disease, diabetes, etc.)
- subject is taking systemic medications that may confound the outcome of the study or increase the risk to the subject, including, but not limited to steroids, antimetabolites, etc.
- subject has history of corneal disease (e.g., herpes simplex, herpes zoster keratitis, etc.)
- subject has had previous intraocular or corneal surgery that might confound the outcome of the study or increase the risk to the subject
- subject has evidence of retinal vascular disease and/or a history of hypercoagulability
- subject has an ocular condition (such as prekeratoconus or keratoconus, recurrent erosion syndrome or corneal dystrophy) that may predispose the subject to future complications
- subject has glaucoma or is suspected of having glaucoma by exam findings and/or family history
- subject of childbearing potential is pregnant, plans to become pregnant, or is lactating during the course of the study, or has another condition associated with the fluctuation of hormones that could lead to refractive changes

6. Surgical Procedure

The clinical protocol should include a description of the surgical procedure, including the power formula to be used and a scientific explanation of its derivation. FDA strongly encourages sponsors to allow personalization of the power formula and to collect this information on the case report forms. The clinical data should be evaluated at intervals during the study to validate the accuracy and to refine the power formula if necessary.

Intraoperative use of viscoelastics and the preoperative, intraoperative and postoperative medications should be standardized in the protocol. Wound placement/size, the use of sutures, and whether an iridectomy/iridotomy is to be performed should also be standardized. If any of these variables are left to the surgeon's discretion, the case report forms should record this information and the final data analysis should include stratification by operative variable(s).

7. Reporting Periods and Evaluations

a. The following reporting periods are suggested:

Preoperative	Month 3 (10-14 weeks)
Operative	Month 6 (21-26 weeks)
Day 1 (1 day)	Month 12 (11-14 months)
Week 1 (5-9 days)	Month 24 (23-27 months)
Month 1 (3-5 weeks)	Month 36 (35-39 months)

b. The following evaluations should be performed (see Annex E for recommended examination schedule):

For all subjects:

- UCVA (distance and near)
- BSCVA (distance and near)

  Note: Sponsors may wish to perform best contact lens corrected visual acuity (BCLVA) on high myopes and hyperopes to increase the accuracy of preoperative refractions and power calculations.

- Manifest and cycloplegic refractions
- Subject questionnaire - should include questions regarding visual symptoms, spectacle/contact lens wear, and functional visual performance (night driving, reading, etc.)
- Intraocular pressure
- Slit lamp exam
- Gonioscopic exam
- Dilated fundus exam – should include exam for the presence of retinal tears
- Mesopic pupil size
- Pachymetry
- Topography (if the cornea may be altered due to the device or the surgical procedure)
- Axial length measurement (preoperatively)
- Anterior chamber depth (ACD) measurement (if inclusion/exclusion criteria include a minimum or maximum ACD)
- Keratometry (to establish preoperative refractive stability for CL wearers and to demonstrate postoperative corneal stability where necessary)
- Assessment of natural lens for cataractogenesis

On a subset of subjects:

- Specular microscopy
- Contrast sensitivity or low contrast acuity testing - mesopic and mesopic with glare conditions

c. Testing Methodologies

i. Visual Acuity

Visual acuity testing should be performed using a logarithmic chart, e.g., ETDRS or equivalent. The same type of chart and testing distance should be used for all testing centers. The chart background luminance should be approximately 85cd/m^2 (80-160 cd/m^2 is acceptable), and should be identical for all testing centers within an IDE study. Ambient illumination should be from dim to dark. No surface (including reflective surfaces) within the subject's field of view should exceed the chart background in luminance.

Refractions should be expressed using the following conventions. Hyperopia with hyperopic astigmatism should be expressed as + sphere + cylinder. Myopia with myopic astigmatism should be expressed as – sphere – cylinder.

ii. Specular Microscopy

Maintenance of endothelial cell counts is considered to be the primary safety endpoint for studies of refractive implants. FDA's main concern is the possibility of a chronic loss of endothelial cells, that, even at a low yearly rate could, over time, lead to corneal edema and decompensation. FDA has estimated that with an initial loss due to surgical trauma of 10% or less, a subsequent yearly loss of 1.5% or less should preserve the integrity of the cornea over the life of the subject.

To determine endothelial cell loss, specular microscopy should be performed preoperatively and at the Month 3 (or Month 6), Month 12, Month 24, and Month 36 exams. Losses due to surgical trauma may be determined by evaluating the cell counts at Month 3 (or Month 6) in comparison to the preoperative measurements. To determine losses over time, measurements from the Month 3 (or Month 6) and later time points should be analyzed.

A yearly rate of cell loss may be determined by subtracting the measurement at Month 3 from the measurement at Month 36 and dividing by 2.75 years (using Month 6 data, divide by 2.5 years). However, to apply this rate of loss to the remainder of the life of the device requires an assumption that the loss of cells after Month 3 (or Month 6) occurs in a linear fashion. Therefore, the sample size chosen for this study should be sufficient to detect a yearly loss of 1.5% as well as to demonstrate the linearity of the cell loss over time (see Section 9 below).

<u>Collection of data</u>
Prior to the beginning of the study, each investigational site should provide a set of consecutive images to the study monitor or sponsor to determine the current state of image quality and to rectify any problems. Cameras that output 35 mm slides, half-inch video, digitized images on disk or images sent by e-mail are acceptable. Cameras that can record digitized images on disk or to e-mail are preferable (for ease of data transfer).

Each site not using an internally calibrated camera (in which each image displays the calibration) should receive a calibration slide that defines both the X and Y axis; instructions on how to obtain the calibration image should be included. Calibration should be checked by the study monitor on at least a yearly basis. Additionally, periodic validation of the study site's methodology should be performed by the study monitor unless an automated camera is used. Calibration of the specular microscopes at the sites across the study should be performed by comparing cell density data from a standard set of images evaluated by

each site. Different cameras may be used, but greater uniformity is expected with a single camera type.

A reading center is advisable, although not required. However, if a reading center is not used, the person responsible for taking and accepting the images should be certified for his/her ability to take high-quality images, and be adequately trained in both endothelial cell photography and in the evaluation of the images. If possible, the same trained and certified technician/photographer should be used at each site throughout the study. A backup technician who is trained and certified should also be available. At least 50 countable endothelial cells should be present in each image; two images from each subject are strongly recommended. The technician/photographer should use a standardized counting method for the determination of cell density. Fixed-frame analysis, variable frame analysis, a center method, a corner method, or auto-count may be used.

iii. Contrast Sensitivity

Contrast sensitivity or low contrast acuity testing should be performed under mesopic and mesopic with glare conditions. Contrast sensitivity should be measured at spatial frequencies as close as possible to 1.5, 3, 6, 12, and 18 cycles/degree. Low contrast acuity should be measured with charts with contrast levels as close as possible to 5%, 10%, and 50%. Subjects should be tested with BCLVA preoperatively, to prevent spectacle distortion and magnification/minification effects from biasing the results.

The chart luminance should be 3 cd/m^2 or less and the ambient illumination should be lower than the chart luminance. In order to limit pupil constriction and maintain uniform glare conditions across the test chart, the glare source should be an array of two or more small spots symmetrically positioned around the chart. The level of glare should be the minimum necessary to significantly reduce the contrast sensitivity of young adult subjects with normal corneas and normal vision, but the illumination should not be so great as to completely wash out the target in these young, normal subjects. The reduction in contrast sensitivity due to glare in normal subjects should be a mean loss of between 0.15 and 0.45 log units at 6 cycles/degree (for grating charts) or an approximate two line loss on a letter acuity chart of approximately 10% contrast. A small pilot study of normal subjects may be necessary to determine an appropriate glare level.

Control data may be obtained from preoperative measurements of best spectacle-corrected noncataractous eyes or from a sample of normal subjects with the same age, gender and refractive error distributions as the postoperative test subjects. The subject population should be large enough to detect a 0.3 log unit difference in contrast sensitivity. (See Section 9 for sample size calculations.)

iv. Evaluation of the Natural Lens for Cataractogenesis

The natural lens should be evaluated preoperatively and at each of the postoperative intervals for lens changes, including, but not limited to, the development of clinically significant lens opacities. A standardized grading system (e.g., Oxford or LOCS III - references below) and photographs are recommended to document lens changes.

Sparrow et al. The Oxford modular cataract image analysis system. Eye 1990; 4:638-48.

Chylack et al. The lens opacities classification system III. The longitudinal study of cataract study group. Arch Ophthalmol 1993; 111:831-6.

v. Mesopic Pupil Size

Pupil size should be measured for all eyes in the study, with eye illumination identical to that used for mesopic contrast sensitivity testing. The measurements should be made with an infrared pupilometer or other calibrated infrared camera. Contrast sensitivity and pupil measurement should begin only after the eye has had time to fully adapt to the testing conditions (approximately 10 minutes).

vi. Slit Lamp Exam

The slit lamp exam should include the measurement of aqueous cell and flare by a standard grading system, a gonioscopic exam, and evaluation for the presence of corneal edema, pupillary irregularities, iris atrophy and pigment dispersion.

The following system is recommended for grading of aqueous cell and flare using a slit beam 0.3 mm wide and 1.0 mm long:

<u>Cells</u>		
none	(0)	= no cells seen
mild	(+1)	= 1-5 cells seen
moderate	(+2)	= 6-15 cells seen
severe	(+3)	= 16-30 cells seen
very severe	(+4)	= > 30 cells seen
<u>Flare</u>		
none	(0)	= No Tyndall effect
mild	(+1)	= Tyndall effect barely discernible
moderate	(+2)	= Tyndall beam in anterior chamber is moderately intense
severe	(+3)	= Tyndall beam in anterior chamber is severely intense
very severe	(+4)	= Tyndall beam is very severely intense. The aqueous has a white and milky appearance.

vii. Measurement of Intraocular Pressure

Intraocular pressure should be measured using Goldmann applanation tonometry. Other methods may be used with a scientific justification, but the same method should be used throughout the study. Additionally, the development of alternate methods may be necessary for refractive implants that alter the cornea such that commonly used methods may not be accurate.

viii. Patient Questionnaire

A patient questionnaire should be administered to all patients. The questionnaire should include questions regarding glare, halos, double vision, spectacle/contact lens use and night driving. The time of onset of visual symptoms should also be addressed.

At the time this document is being written, there are no validated patient questionnaires specifically addressing refractive surgery issues that have been published. Until references to published validated questionnaires are available, FDA recommends that a validated questionnaire that addresses visual function following ophthalmic surgery be used, with questions specifically relating to refractive surgery issues be written in the same format and added to the questionnaire.

8. Adverse Events

Reports of unanticipated adverse device effects shall be reported to the sponsor and the reviewing IRB within 10 days of the investigator's learning of them, and to FDA and all reviewing IRBs and participating investigators within another 10 days of the sponsor's learning of them (see 21 CFR 812.150(a)(1) and 812.150(b)(1)). All other adverse events shall be documented in the case reports.

The following adverse events, although not an all-inclusive list, should be considered to be reportable as described in 21 CFR 812.150(b)(1).

Endophthalmitis
Pupillary block
Retinal detachment
Corneal ulceration/infectious infiltrate
Stromal thinning/corneal melting
Corneal haze/cloudiness, if associated with ≥ 2 lines BSCVA loss
Secondary surgical intervention*
Extrusion of the device

* Note: Secondary surgical interventions should be reviewed by the sponsor on a case-by-case basis to determine if reporting is appropriate.

Additionally, the sponsor should provide a list of possible adverse events, including any that apply from the list below, that may occur in conjunction with the investigational device. The clinical report forms should include forced-choice listings of these adverse events and allow for the recording of other adverse events not listed.

Hyphema	Epithelial defect
Macular edema	Epithelial inclusion cyst
Corneal scarring	Epithelial ingrowth
Uveitis/Iritis	Corneal haze/cloudiness
Conjunctivitis	Corneal infiltrates - sterile
Raised IOP requiring treatment	Corneal edema
Vitreous loss (intraoperative)	Dislocation of device
Central corneal sensation loss	Induction of cataract
Corneal neovascularization - pannus or deep vessel	

9. Data Analysis/Statistical Methods

a. Sample Size Determination

i. Maintenance of endothelial cell counts

The loss of endothelial cells over time should be determined by evaluating measurements taken at the Month 3 (or Month 6) through Month 36 exams. Two measurements should be taken at each visit and the mean cell count should be used. The number of subjects should be sufficient to detect a yearly endothelial cell loss of 1.5% and to demonstrate linearity of the cell loss over time.

One approach to determining an appropriate sample size is to set an upper bound of the 90% confidence interval (C.I.) around the observed loss using the following formula:

$$\text{Upper 90\% C.I.} = X + Z_{\alpha}(\sigma/\sqrt{N})$$

where X is the observed total cell loss after 2.75 years (then divided by 2.75 to calculate the yearly loss), $Z_{\alpha} = 1.28$ for a one-sided upper 90% C.I., σ is the assumed standard deviation of 5%, and N is the sample size.

If the upper bound is set to 4.125% (representing a 1.5% per year loss) and a standard deviation of 5% is assumed, a sample size of 200 subjects would ensure with 90% confidence that the true population loss is 1.5% per year or less. The observed loss must be greater than 1.33% per year for the 90% C.I. to exceed 4.125%. A sample size of 200 subjects should also be sufficient to demonstrate linearity.

ii. Maintenance of Contrast Sensitivity

Contrast sensitivity losses should be determined by comparing measurements obtained at the Month 3 or Month 6 visit (depending upon when refractive stability is demonstrated) and at the Month 36 visit with preoperative measurements. The sample size should be sufficient to detect a 0.3 log unit loss, assuming a 0.2 log unit standard deviation. Tolerance limits may be used to establish with a certain level of confidence (e.g., 90%) that a reasonable percent (e.g., 95%) of the

population has losses below the largest observed value in the sample (hopefully, 0.3 log units).

If the tolerance limit is set to ≤0.3 log units, then assuming $\bar{x} = 0$ (under the null hypothesis of no loss) and $s = 0.2$, solving for K in the following equation:

$$\bar{x} + Ks \leq 0.3$$

$$0 + K(0.2) \leq 0.3$$

$$K = 1.5$$

Using this value for K, with appropriate statistical tables, an estimated sample size of approximately 80 would afford about 90% confidence that 95% of the losses would be below 0.3 log units. Since the value of 80 is an estimate, FDA recommends enrolling 125 subjects in this substudy.

b. Accountability

For further information, sponsors are referred to FDA's draft guidance document, "Accountability Analysis for Clinical Studies for Ophthalmic Devices" (Federal Register notice dated August 4, 1999, http://www.fda.gov/cdrh/ode/1350.pdf).

A PMA should not be submitted until at least 80% of subjects enrolled have become eligible for the final visit (i.e., 20% or fewer subjects remain active).

Tables showing the overall accountability (at the last visit) and accountability by postoperative visit should be presented. Suggested formats follow:

Overall Accountability

	Total	Percentage n/N
Enrolled (N)		
Available for Analysis		
Day 1		
Week 1		
.		
.		
.		
Missing subjects at (final visit)		
Discontinued		
Missing (final visit) but seen at a later visit		
Not seen but status obtained (e.g., by phone)		
Lost to follow-up		
Active		

Accountability by Postoperative Visit

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Available for Analysis n/N (%)					
Discontinued n/N (%)					
Active n/N (%)					
Lost to follow-up n/N (%)					
% Accountability = Available for Analysis / (Enrolled-Discontinued-Active)					

N = total eyes enrolled

c. Data Presentation/Analyses

The following analyses, although not an inclusive list, are recommended for submission in the PMA.

i. Stability of Manifest Spherical Equivalent Refraction (MRSE)

The sponsor should calculate the number of subjects who have:

- a change of less than or equal to 1.00 D of MRSE between two refractions performed at least 3 months apart
- a change of less than or equal to 0.50 D of MRSE between two refractions performed at least 3 months apart

The sponsor should calculate the mean change in MRSE between visits as determined by a paired analysis. This value should ideally be 0.025 D per month or less.

ii. Maintenance of Endothelial Cell Counts

The sponsor should perform the following analyses:

- mean rate of cell loss over time, calculated via a paired analysis in order to calculate the mean of the differences
- frequency analysis examining the percentage of patients who lose greater than 10% of cells between Month 3 (or Month 6) and Month 36

iii. Evaluation of the Natural Lens for Cataractogenesis

Analyses should include:

- the percentage of subjects with lens changes (i.e., any change in the appearance of the lens, with stratification by the type of change)

- the percentage of subjects with clinically significant lens opacities (defined as opacities leading to a loss of 2 or more lines of BSVCA with glare as compared to preoperative levels adjusted for magnification/minification effects)

iv. Maintenance of Contrast Sensitivity

The sponsor should perform the following analyses:

- at each spatial frequency (or at each contrast level for low contrast acuity testing), the mean change in contrast sensitivity/acuity between preoperative and postoperative measurements as determined by paired analyses
- the number of subjects who have a loss >0.3 log units at two or more spatial frequencies
- at each spatial frequency or contrast level, the results with glare versus without glare
- results stratified by mesopic pupil size

v. Additional Analyses

The following additional analyses are recommended:

- Preoperative demographics - gender, race, eye treated (left or right), age, contact lens history
- Dataline subject listings of protocol deviations
- Last reported status (UCVA, BSCVA, MRSE) of discontinued subjects (excluding subjects who were retreated)
- Last reported status (UCVA, BSCVA, MRSE) of lost to follow-up subjects
- Summary of the safety and effectiveness variables listed in B.3 above by exam (including 95% C.I. for each value)
- Change in BSCVA at each exam, stratified by lines of loss or gain (+1, +2 >+2, -1, -2, >-2) with dataline listings for those subjects who lost 2 or more lines
- UCVA at each visit - stratify by intended postoperative refraction (emmetropia vs. intentional undercorrection)
- Change in IOP from preoperative levels (increase 1-5, 6-10, >10 mmHg, and decrease 1-5, 6-10, >10 mmHg)
- For cylindrical corrections:
  - accuracy of spherical component and accuracy of cylindrical component
  - stability of MR cylinder
  - subjects with residual astigmatic error

Annex E
(informative)

Recommended Postoperative Examination Schedule

	Preop	Op	Day 1	Week 1	Month 1	Month 3	Month 6	Month 12	Month 24	Month 36
Distance UCVA	X		X	X	X	X	X	X	X	X
Distance BSCVA	X			X	X	X	X	X	X	X
Near UCVA	X			X[2]	X[2]	X[1,2]	X[2]	X	X	X
Near BSCVA	X			X[2]	X[2]	X[1,2]	X[2]	X	X	X
Manifest refraction	X	X[3]		X	X	X	X	X	X	X
Cycloplegic refraction	X							X	X	X
Axial length	X									
Intraocular pressure	X	X[4]	X	X	X	X	X	X	X	X
Slit lamp exam	X		X	X	X	X	X	X	X	X
Gonioscopic exam	X						X	X	X	X
Dilated fundus exam	X				X			X	X	X
Mesopic pupil size	X						X[5]			X
Pachymetry	X	X[6]					X			X
Keratometry[7]	X	X						X		X
Topography[8]	X				X		X			
Subject questionnaire	X						X	X	X	X
Contrast sensitivity	X					X[9]	X[9]			X
Specular microscopy	X					X[9]	X[9]	X	X	X

1 - for hyperopia protocols
2 - for presbyopia protocols
3 - for contact lens wearers
4 - post-surgery operative day IOP measurements should be considered if pupillary block is a possible complication
5 - should be performed at the same visit as contrast sensitivity testing

6 - if required for the surgical procedure
7 - to establish preoperative refractive stability for CL wearers and to demonstrate postoperative corneal stability where necessary
8 - for devices that are intended to alter the cornea
9 - these tests may be performed at either the Month 3 or the Month 6 exam, but must be performed at the same exam for all subjects